Unresolved issues in perioperative nutrition: A narrative review

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ABSTRACT

Surgical patients are at an increased risk of negative outcomes if they are malnourished or at risk of malnutrition preoperatively. Optimisation of nutritional status should be a focus throughout the perioperative continuum to promote improved surgical outcomes. Enhanced Recovery after Surgery (ERAS) protocols are increasingly applied in the surgical setting but are not yet widespread. This narrative review focused on areas of perioperative nutrition that are perceived as controversial or are lacking in agreement. A search for available literature was conducted on 1 March 2022 and relevant high-quality articles published since 2015 were considered for inclusion. Most malnutrition screening tools are not specific to the surgical population except for the Perioperative Nutrition Screen (PONS) although more large-scale initiatives are needed to improve the prevalence of preoperative nutrition screening. Poor muscle health is common in patients with malnutrition and further exacerbates negative health outcomes indicating that prevention, detection and treatment is of high importance in this population. Although a lack of consensus remains for who should receive preoperative nutritional therapy, evidence suggests a positive impact on muscle health. Additionally, postoperative nutritional support benefits surgical outcomes, with some patients requiring enteral and/or parenteral feeding routes and showing benefit from immunonutrition. The importance of nutrition extends beyond the time in hospital and should remain a priority post-discharge. The impact of individual or personalised nutrition based on select patient characteristics remains to be further investigated. Overall, the importance of perioperative nutrition is evident in the literature despite select ongoing areas of contention.

KEYWORDS: immunonutrition; muscle; muscle health; nutritional interventions; nutritional screening; perioperative nutrition

1. Introduction

Nutritional status is an important determinant of outcomes after surgical operations ever since Studley, in 1936, showed that patients with a preoperative weight loss of ≥20% were 10 times more likely to die after surgery for peptic ulcer than those who had lost <20% body weight [1]. Since then, there has been an increased awareness of the adverse effect of malnutrition on surgical outcomes and the need for nutritional therapy in the perioperative and post-discharge phases to help reduce muscle loss and promote anabolism. Although Enhanced Recovery after Surgery (ERAS) protocols have become the standard of perioperative care [2], these protocols do little to prevent muscle loss as apart from early feeding, nutritional interventions are not emphasised. Even though low muscle mass and quality is an independent predictor of poor surgical outcomes, perioperative nutrition is still a neglected area world-wide and despite the publication of evidence-based guidelines and monographs [3-5], it does not get the clinical attention that it deserves. In this narrative review, we aimed to concentrate on areas of perioperative nutrition that are perceived as controversial or are lacking in agreement and present an evidence-based argument that may help improve the nutritional care of the surgical patient, as summarised in **Figure 1**.

2. Methodology

We searched PubMed, Web of Science, Google Scholar and Cochrane Library databases on 1 March 2022 using the terms “perioperative nutrition”, “surgical nutrition”, “body composition”, “sarcopenia”, “sarcopenic obesity” and “myosteatosis” in combination with one or more of the following keywords: “causes”, “pathophysiology”, “outcomes”, “complications”, “mortality”, “guidelines”, “discharge”, “education”, “hospital”, and “inpatient”. We identified articles on adult surgical patient populations and selected the most relevant clinical trials, meta-analyses, systematic reviews, cohort studies, high-quality review articles and guidelines published since January 2015. We also hand searched reference lists of identified articles to retrieve additional studies. Preference was given to the most relevant research, but we also selected publications that showcased particular areas of interest. We have concentrated on issues in perioperative nutrition that are either currently controversial or unresolved.

3. Epidemiology

Studies from the United States and Europe show that up to a third of all patients admitted to hospital are either malnourished or at risk of malnutrition [6]. Nutritional status often deteriorates during hospital stay due to illness-related loss of appetite, drug-related side-effects, fasting orders for diagnostic studies, diseases that impair the normal functioning of the digestive system, overall suboptimal management of inpatient nutrition, and disease- and disuse-related wasting [6]. However, a recent review suggested that two-thirds of patients scheduled for gastrointestinal surgery are malnourished at the time of admission and that these patients have a three-fold increase in risk of developing postoperative complications and a five-fold greater risk of mortality than well-nourished patients [5]. More worryingly, the review found that only one in five hospitals in the Western world had formal nutritional screening processes in place and that only one in five patients received any form of preoperative nutritional intervention. Nevertheless, when nutritional therapy was instituted, every dollar spent on this resulted in a $52 (USD) saving in hospital costs [5]. In addition, a meta-analysis of five studies from the United Kingdom investigating outcomes after abdominal surgery showed that the use of oral nutrition supplementation (ONS) in the hospital setting resulted in a mean net cost saving of £746 per patient [7]. Besides overt protein-calorie malnutrition, a significant proportion of patients may also have undetected micronutrient-related malnutrition [6]. Disease-related inflammation is exacerbated by the metabolic response to surgical trauma [8-10], which can cause further deterioration in nutritional status [9].

4. Identifying the surgical patient in need of nutritional therapy

Screening for malnutrition is a first and crucial step for identification of patients who could benefit from nutritional therapy. There is wide consensus that screening for malnutrition should be performed within the first 24-48 hours of admission to hospital. This gives the professional care team enough time to perform further nutritional assessment and refer patients to a specialist team for nutritional intervention as needed [11]. Particularly for the elective surgical patient, screening for malnutrition prior to surgery can identify patients at risk for malnutrition who may benefit from preoperative nutritional intervention. Ideally this should be done at first contact with the patient (e.g., in the outpatient clinic) so that necessary interventions may be instituted well in time for surgery. Several malnutrition screening tools exist to detect potential or manifest malnutrition upon hospital admission in surgical and medical patients [6, 12-14]. **Table 1** provides an overview of select nutritional risk screening tools for adults [5, 13, 15-24].

While these screening tools have been validated mostly for use in hospitalised medical and surgical patients, there is currently no universally accepted tool for preoperative malnutrition risk screening. Another more specific malnutrition screening score for the surgical patient in the preoperative setting is the Perioperative Nutrition Screen (PONS) [5]. PONS is a similar instrument to the Malnutrition Universal Screening Tool (MUST) but was adapted specifically for the preoperative surgical patient. It identifies nutritional risk based on several parameters including low body mass index (BMI) (<18.5 kg/m^2 or <20 kg/m^2 if >65 years), unintentional weight loss (>10% in 6 month), low intake during the preceding week (<50% of normal diet) and/or low albumin concentration (<30 g/L). Patients with at least one point are considered to be at high risk for perioperative malnutrition.

Although there are no large comparative studies of screening tools in surgical patients, a recent study compared Nutrition Risk Screening 2002 (NRS 2002), Subjective Global Assessment (SGA), Short Nutritional Assessment Questionnaire (SNAQ), Mini Nutritional Assessment (MNA) and MUST in medical patients [25]. The authors showed that with all five screening and assessment instruments, higher nutritional risk was associated with higher risk for mortality and adverse clinical outcome, but not with treatment response from nutritional support [25]. However, NRS 2002 and SGA showed the most pronounced relationship between the severity of malnutrition and reduction in mortality as a response to nutritional support [25].

After the screening of patients, the next important step is to apply more specific diagnostic criteria to confirm malnutrition. The Global Leadership Initiative on Malnutrition (GLIM) has recently published such criteria which include phenotypic criteria (unintentional weight loss, low BMI, and reduced muscle mass) and aetiological criteria (reduced food intake or assimilation, and inflammation or disease burden) [26, 27]. While most studies on GLIM criteria have focused on medical patients, there is also increasing literature looking at the surgical patient [28].

5. Improving nutritional screening for surgical patients

Despite available tools and recommendation to screen all pre-surgical patients [4], nutritional screening is not universal. Even in the 21st century, a proportion of patients do not have a BMI recorded in their medical chart. One study showed that up to 4% of patients had no screening at all, 9% did not have body weight measured and over 30% did not have a BMI calculated [29]. Screening tools are efficient and effective yet only 80% of hospitalised patients are screened. In the United Kingdom, only two thirds of respondents reported a formal preoperative nutritional screening process in their surgical departments [30]. Nutritional screening at admission needs to be enforced in hospitals to ensure that every surgical patient can have their nutritional status optimised and benefit from the effectiveness of enhanced nutrition preoperatively.

Consensus pathways that include nutritional screening exist but are not widely implemented in surgical settings [31-34]. In Canada, the Integrated Nutrition Pathway for Acute Care (INPAC) was successfully implemented and sustained in medical and acute care settings and increased nutritional screening of patients admitted for surgery [35, 36]. Nutritional screening upon admission increased from 50% to 84% of patients after INPAC was integrated into medical and surgical settings and presents a viable approach for further scaling implementation of screening processes [32]. In the United States, a dietitian-driven multidisciplinary team (Perioperative Enhancement Team) clinic was designed to screen for preoperative malnutrition and optimise nutritional support for those in need [37]. If proven successful, this may present as another viable option for further spread and scale. In Portugal, nutritional risk assessment was made mandatory and systematically integrated for all patients admitted to national hospitals in 2019 and resulted in an increased proportion of patients screened for malnutrition risk [38].

6. The role of skeletal muscle in surgical outcome

Body composition should be considered when evaluating the nutritional status of the surgical patient. Patients may present with low muscle mass prior to surgery due to ageing and/or a pre-existing disease. Research on the prognosis of muscle mass on surgical outcomes has increased exponentially in recent years [39], highlighting that low muscle mass is prevalent and an independent predictor of surgical outcomes. Notably, the majority of studies have relied on cross-sectional measurements of skeletal muscle mass utilising computerised tomography imaging (CT), due to their frequency of availability in patients' medical records.

As reviewed by Yokoyama et al. [39], studies in different surgical contexts such as oesophagectomy, colectomy, pancreaticoduodenectomy, major hepatectomy, and liver transplantation have confirmed the negative short and long-term outcomes related to poor muscle health. Notably, the majority of studies have been performed in the context of surgical oncology due to availability of CT images in patients' medical records, and the high prevalence of muscle wasting among these patients [40]. In a meta-analysis of 70 studies in patients with gastrointestinal cancer, low muscle mass was associated with an increased risk of complications (RR: 1.19; 95% CI: 1.08 to 1.30), major complications (RR: 1.23; 95% CI: 1.04 to 1.45), overall mortality (HR: 1.60; 95% CI: 1.37 to 1.87), and disease-free mortality (HR: 1.46; 95% CI: 1.29 to 1.65) [41]. In another meta-analysis including 27 studies in patients with head and neck cancer, low muscle mass was associated with severe postoperative complications (OR: 4.79; 95% CI: 2.52 to 9.11), disease-free survival (HR: 1.64; 95% CI: 1.33 to 2.03), and lower overall survival (HR: 1.87; 95% CI: 1.53 to 2.29) [42].

In addition to muscle mass, low muscle quality (indicated by decreased radiodensity on CT scanning), which is reflective of fat infiltration into muscle (or myosteatosis) is also associated with negative outcomes. Xiao et al. [43] showed that low muscle radiodensity was associated with a higher risk of major complications in patients with early-stage colorectal cancer. Additionally, patients with both low muscle radiodensity and low muscle mass had a higher 30-day mortality risk [43]. In another study, patients with inflammatory bowel disease and myosteatosis had a longer length of hospital stay and a higher prevalence of 30-day readmission [44]. This condition has also been shown to associate with shorter survival in patients with pancreatic cancer [45].

Surgery induces a catabolic environment due to endocrine, metabolic, and immunological changes, and an impairment in muscle mitochondrial function [8-10]. These changes are exaggerated in patients presenting with pre-existing/at-diagnosis low muscle mass and can be exacerbated by bed rest [46]. As such, skeletal muscle can be rapidly lost after surgery. Otsuji et al. [47] explored the association of the lowest tertile of muscle loss with clinical outcomes in patients undergoing major hepatectomy. Despite the limitations of using a single muscle (versus the entire muscle cross-sectional area) measurement [48], muscle loss was an independent factor for major complications (OR: 3.21; 95% CI: 1.82 to 5.76) [47]. Another study showed a rapid decline in trunk muscle size for inpatients who underwent general surgery [49]. Patients in the tertile of the greatest loss had an increased risk of 1 year mortality (OR: 3.4; 95% CI: 1.55 to 7.47) [49]. In patients undergoing gastrectomy, losing 10% or more of muscle cross-sectional area was associated with a higher incidence of postoperative complications, decrease in grip strength, longer length of hospital stay, higher costs, and poorer quality of life related to fatigue and physical functioning at 1 and 3 months postoperatively [50]. Accelerated muscle loss in patients undergoing resectional surgery for pancreatic cancer has also been reported by Choi et al [51]. In this study, muscle loss greater than 10% over 60 days was an independent predictor of shorter survival [51].

Changes in body composition, particularly skeletal muscle mass, must be interpreted with caution due to the measurement error of assessment techniques and the ability to detect small changes over time. With this limitation in mind, collectively, multimodal prehabilitation interventions, which include nutrition and physical exercise, have been shown to protect or improve muscle mass (or its related compartments i.e., lean soft tissue and fat-free mass). Given the importance of muscle and integration of physical therapy/exercise in multimodal prehabilitation, functional status screening at time of admission in conjunction with nutrition risk screening is likely warranted.

7. Preoperative nutritional therapy and prehabilitation

The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline on clinical nutrition in surgery states that nutritional therapy is indicated in patients with malnutrition and in those at risk of malnutrition. It also states that nutritional therapy should be initiated if the patient will not be able to eat for five days perioperatively or it is anticipated that the patient will not be able to eat more than 50% of required calories for more than seven days [4]. The updated ERAS Society guideline recommends oral food supplementation preoperatively for 7-10 days in patients with colorectal cancer if there is a metabolic risk or evident nutritional deficit [52]. The ESPEN guideline on clinical nutrition in surgery [4] definition of high metabolic risk includes: weight loss of >10-15% within 6 months, BMI <18.5 kg/m^2, SGA Grade C or NRS score >5, preoperative serum albumin <30 g/L (in absence of liver or kidney impairment). In patients with high metabolic risk, nutritional therapy should be initiated without delay, depending on the degree of malnutrition, the planned operation and the foreseeable period of insufficient food intake. In the case of neoadjuvant treatment, nutritional status should be monitored to ensure that weight loss or deterioration of nutritional status must be avoided. In patients treated with neoadjuvant therapy, the preoperative break is particularly suitable for surgical conditioning.

The more recent concept of prehabilitation covers the period of 4-6 weeks prior to surgery [53]. The exact mechanisms of prehabilitation on postoperative systemic inflammatory response are yet to be elucidated. When comparing prehabilitation with conventional rehabilitation alone, additional prehabilitation may be more effective for attenuating postoperative complications [54] although this is not the case in all populations (e.g., frail older adults) [53]. Nutritional therapy is just one of many pillars including physical therapy/exercise and psychological intervention that are used to optimise patients' status prior to surgery. The aim is also to make older, functionally impaired patients "fit" for surgery [55, 56]. There are currently no precise recommendations for the organisation and implementation of prehabilitation; programmes vary widely in terms of duration, content, and frequency of individual measures.

Uni- or multimodal prehabilitation has been investigated in numerous trials. Due to the heterogeneous protocols, aggregated results in several meta-analyses have been inconsistent, **Table 2** [57-59]. Daniels et al. [57] included 33 studies with 3962 patients with two or more prehabilitation interventions in their review of older patients with surgery for an abdominal tumour. With targeted nutritional therapy alone (risk difference: -0.18; 95% CI: -0.26 to -0.10; p<0.001, I^2 = 0%) the meta-analysis showed an advantage for reducing the rate of surgical complications [57]. Assouline et al. [58] pooled 2070 patients from 29 studies for their meta-analysis. Compared with the control group, the prehabilitation group had a lower incidence of postoperative pulmonary complications (RR: 0.52; 95% CI: 0.41 to 0.66), although the evidence was rated as moderate [58]. A recent meta-analysis of 22 randomised studies in patients undergoing major oncological surgery showed a significant improvement in functional capacity, measured by the 6-minute walk test (mean difference: 33.09 m; 95% CI: 17.69 to 48.50 m; p<0.01) which was associated with shorter length of hospital stay (3.68 days; 95% CI: 0.92 to 6.44; p=0.009) [59]. No differences were found for the rate of general and pulmonary postoperative complications shown in other meta-analyses. Hospital readmission rate and mortality were also unaffected [59].

A pooled analysis of two randomised clinical trials of trimodal prehabilitation versus trimodal rehabilitation showed that the first attenuated post-surgical losses of fat-free mass compared with the second group. The interventions consisted of exercise, nutrition, and anxiety-reduction elements starting approximately 4 weeks before surgery and continuing for 8 weeks after surgery [60]. Fat-free mass was estimated using a proprietary bioelectrical impedance analysis equation. In another study using CT images, Allen et al. [61] showed that patients with locally advanced oesophagogastric cancer receiving 15 weeks of prehabilitation (versus usual care) presented with less muscle loss [−11.6 (95% CI: −14.2 to −9.0) *vs*. −15.6 (95% CI: −18.7 to −15.4) cm^2/m^2; p=0.049]. Although muscle loss was attenuated in the prehabilitation group, the intervention did not preclude the development of sarcopenia (prehabilitation group: +16%; control group: +38%; p=0.404). The intervention involved twice-weekly supervised exercises, thrice-weekly home exercises, and psychological coaching [61]. Improvement in functionality, nutritional status and quality of life that can be achieved through prehabilitation has been clearly demonstrated and emphasize the need for widespread multimodal prehabilitation.

Home-based prehabilitation, carried out independently by the patient according to prior teaching or virtual coaching [62, 63] can generally be recommended at low cost before major operations. So far, evidence is weak for a significant reduction in the rate of complications. This is likely due to the many statistically "underpowered" studies. It may be possible that high-risk patients with considerable functional and nutritional deficiency, who are not good candidates for inclusion in studies, benefit most from individualised and supervised multimodal prehabilitation. For these patients, data from controlled studies remains limited [57] although there are ongoing studies of patients undergoing colorectal resections [64-66], gastrectomy [67], and oesophagectomy [68, 69].

8. Postoperative nutritional therapy

Based on evidence, early oral food intake, even after colorectal resections, has received a strong recommendation in the ESPEN guideline on clinical nutrition in surgery [4]. The diet should be adapted to the individual tolerance and the performed operation with patients who are older adults requiring special attention [4]. Delaying re-integration of diet offers no advantages and may lead to an increased rate of infectious complications [70], mortality [71], and longer hospital stays [72]. A critical question has been whether early oral administration is also feasible and safe after gastrectomy and esophagectomy.

In a randomised, multi-centre study, the feasibility and safety of early oral nutrition after minimally invasive oesophagectomy with intrathoracic anastomosis was investigated [73]. In the intervention group (n=65) the oral diet was initiated without delay, while the control group (n=67) was fed exclusively via enteral tube for 5 days. There was no significant difference in the primary endpoint of postoperative recovery (7 *vs*. 8 days) and the secondary endpoints complications, anastomotic insufficiency (18.5% *vs*. 16.4%) and rate of pneumonia (24.6% *vs*. 34.3%) [73]. In another retrospective study using propensity score matching, gastrectomy patients who received early oral diet from postoperative day one (EOF n=203) were compared with historical controls who received a traditionally delayed diet (COF n=203) [74]. The EOF group showed an earlier onset of flatus (2.9 *vs*. 3.1 days, p=0.013), length of hospital stay was significantly shorter (8.9 ± 5.7 *vs*. 12.6 ± 10.2 days, p<0.01), and there was no difference in morbidity and mortality, with the EOF group developing a lower rate of abdominal infections (3.0% *vs*. 7.4%, p=0.044) and anastomotic leakages (1.5% *vs*. 4.9%, p=0.048) [74]. A subgroup analysis based on age, sex, surgical technique, lymph node dissection and tumour stage did not reveal an increased risk of morbidity, including the development of anastomotic leakage, with early oral feeding. Adherence with oral nutrition was indistinguishable between groups [74].

In a prospective study of patients who underwent major abdominal surgery (n=50), protein and energy consumption were recorded in the first week postoperatively [75]. Energy and protein intake was considered insufficient at <25 kcal/kg body weight and <1.5 g/kg, respectively for more than 2 days in the first postoperative week. In most patients, energy (82%) and protein intakes (90%) were inadequate. In addition, more Clavien-Dindo III complications were observed in the patients who did not achieve the protein target [75]. From a nutritional point of view, early oral feeding is feasible, but in favour of enteral supplementation jejunal tube implantation or even fine needle catheter jejunostomy may be considered during surgery.

In terms of parenteral nutrition, the Good Clinical Practice recommendation of the ESPEN guideline on clinical nutrition in surgery states that if oral and enteral energy and nutrient intake cannot cover more than 50% of requirements for more than 7 days, a combination of enteral and parenteral nutrition is recommended [4]. This makes monitoring and documentation of oral food intake mandatory in an ERAS protocol to avoid permissive undernutrition. In everyday clinical practice, parenteral nutrition will be indicated in patients with prolonged recovery. This may be due to limited gastrointestinal tolerance, delayed gastric emptying, and/or complications requiring reoperations with the need for long-term intensive care treatment. Additionally, artificial nutrition should be considered when energy and protein requirements are anticipated to not be met in the early postoperative period.

Gao et al. [76] randomised patients (n=230) who underwent abdominal surgery, were at increased nutritional risk, and had poor tolerance to enteral nutrition postoperatively to early (postoperative day 3) or late (postoperative day 8) supplemental parenteral nutrition. Patients who received early parenteral nutrition were at significantly lower risk of hospital-acquired infection (risk difference: 9.7%; 95% CI: 0.9 to 18.5; p=0.04) although no difference was observed for secondary outcomes including infectious complications, adverse events, length of hospital stay, and cost of admission [76]. Although early parenteral nutrition showed some health benefits is this group of surgical patients, further treatment details are needed to interpret these findings [77]. As described by Ljungqvist et al. [77], these findings are difficult to compare to ERAS protocols and other similar studies given that the average length of hospital stay (~17 days) in this cohort of patients exceeded the typical length of an ERAS protocol [76]. Further, preoperative interventions aimed at the physical, nutritional, and psychological components of overall health should be clearly described along with postoperative adherence to ERAS protocols and any patient or family education provided

[76, 77]. These are factors known to impact postoperative recovery and thus are essential for interpreting perioperative nutritional intervention trials.

9. Post discharge nutrition and exercise

Surgical trauma [78], immobilisation [79], poor nutritional intake [80], malnutrition [81], and pro-inflammatory conditions [82] cause a rapid loss of muscle that requires a significantly longer period to rebuild compared with the timeframe in which it depleted. This process is well explained using the analogy of a wildfire [83]. Exercise supports muscle anabolism capabilities (e.g., increasing muscle capillarisation, protein synthesis, insulin sensitivity, etc.) and is a tool needed to combat muscle loss and support surgical recovery [3]. Resistance exercise training should be combined with targeted energy and protein intake that is sufficient to support the increased metabolic needs observed during recovery [3]. Rehabilitation exercise and nutrition support by community nursing is a key component for ensuring positives outcomes post-discharge [84].

Surgical recovery was traditionally considered complete at time of hospital discharge. In actuality, recovery continues until return to baseline function is achieved or surpassed [85]. Given the high prevalence of patients with elevated nutritional risk or malnutrition preoperatively [86], nutrition and mobilisation should remain a focus beyond the hospital setting and continue when the patient returns home in the community to maximise healing [87].

Patients admitted for surgery, especially those with cancer, often have other comorbidities that impact muscle [88] and subsequently nutritional status, therefore challenging the effectiveness of nutritional support in the perioperative period. Thus, marginal gains achieved from nutrition care should not be discounted. When considered cumulatively, small gains are likely to surmount to clinically meaningful outcomes, especially when nutrition is optimised throughout the pre-, peri-, postoperative, and post-discharge phases, as shown in **Figure 2** [87].

Nutritional supplementation is recommended upon discharge [4, 5, 89-91] despite not being a standard of care. Such intervention is often doubted and seen as an afterthought, perhaps due to the limited and conflicting evidence of benefit [91-94]. Meng et al. [95] investigated the effects of post-discharge ONS on nutrition-related outcomes in patients with nutritional risk who were discharged following surgical resection for gastric cancer. Average ONS intake in the intervention group was 370 ml/day and resulted in significantly less weight loss and a higher BMI and muscle mass. Smaller rates of low muscle mass, changes to treatment (i.e., delays, reductions, terminations), and less fatigue and loss of appetite were also seen in the ONS group. Similar findings were observed in patients with nutritional risk who were receiving ONS after discharge from hospital subsequent to colorectal cancer resection [96]. Patients who received ONS post-discharge had significantly higher muscle, lower rates of low muscle mass, and less changes to their chemotherapy regimen, although no differences in weight loss, BMI, fatigue, or loss of appetite were observed [96].

A systematic review of 18 studies showed a postoperative weight loss of 5-12% within 6 months in patients after oesophageal resection. More than half of the patients lost >10% body weight [97]. The ESPEN guideline on clinical nutrition in surgery recommends implantation of a feeding tube during surgery, with the fine needle catheter jejunostomy offering the option of long-term post-discharge supplementation and improved weight trajectory [4]. A study of post-discharge continuation of enteral nutrition after oesophageal and gastric resection, as well as pancreaticoduodenectomy, nonetheless found that perioperative weight loss was >10% in 40% of the patients (n=35) [98].

Restricted adherence for ONS is expected [99] and may be related to loss of appetite, taste, belching, gas and diarrhoea. By continuing enteral supplementation, body weight is more likely to stabilise after 4-6 months [98]. A recent meta-analysis of 15 randomised controlled trials with 1059 patients addressed the question of home enteral nutrition versus ONS. Home enteral route nutrition (HERN), normal oral diet and ONS were compared in patients with upper gastrointestinal resections [100]. Home enteral nutrition resulted in less weight loss (-3.95 *vs*. -5.82 kg; standardised mean difference: 1.98 kg; 95% CI: 1.24 to 2.73) and malnutrition or latent malnutrition (RR: 0.54; p<0.01) compared with normal oral diet. Weight loss in the HERN group was significantly lower than in the normal oral diet group without supplementation (weighted mean difference [WMD]: 2.69, p<0.01). The HERN group presented with superior physical function (WMD: 5.29; 95% CI: 1.86 to 8.73) and less fatigue (WMD: -8.59; 95% CI: -12.61 to -4.58).

In a multi-centre randomised study of patients (n=1003) after gastrectomy, the effects of ONS with 400 kcal/d on weight loss after one year were compared with the control patients [101]. Weight loss in the intervention group was significantly lower after 3 months but not different after one year. In the ONS group, only 50.4% of the patients consumed more than 200 kcal/day (mean: 301 ml), but after one year they had a significantly lower loss of body weight (8.2 ± 7.2%) than the control group (p=0.020) [101].

10. Immunonutrition

Stimulating the immune system by enriching the diet with suitable substrates has been challenging. The stimulation of antitumoral T cell activity has been shown in vitro for arginine [102]. Anti-inflammatory effects can be expected from the administration of the omega-3 fatty acids eicosapentaenoic and docosahexaenoic acid. This relies on the shift in mediator synthesis to those with lower inflammatory activity, e.g., from leukotriene B4 to B5. Specific anti-inflammatory mediators are resolvins, protectins, and maresins which are synthesised from docosahexaenoic acid and eicosapentaenoic acid [103].

An umbrella review of meta-analyses recently investigated the overall efficacy of perioperative immunonutrition for mitigating postoperative infectious complication (primary outcome) and morbidity, mortality, and length of hospital stay (secondary outcomes) following visceral surgeries [104]. Initiation of immunonutrition at specific timepoints in the operative continuum did not impact outcomes although the use of immunonutrition in general (i.e., at any point within the perioperative period) showed a beneficial effect on postoperative infectious complications.

10.1 Oral / enteral immunonutrition

In particular, the combination of arginine, omega-3 fatty acids and ribonucleotides provided in an enriched oral drink supplement and enterally has shown clinical benefits for reducing the rate of infectious complications, length of hospital stay and costs and may also apply to an ERAS program [105]. Significant improvement in the immune parameters CD4/CD8 ratio, the killer cell rate and the Ig-A serum level has been shown for patients with oesophageal resection compared with standard enteral nutrition, but without any impact on the clinical outcome [106]. Improved long term survival in cancer patients has been discussed for patients with postoperative enteral immunonutrition. A very recent secondary analysis of a previous randomised trial in patients undergoing major surgery for esophagogastric and pancreatiobiliary cancer could not confirm impact on long-term survival for an arginine enriched immunonutrition [107].

The question remains whether exclusively preoperative administration offers advantages not only in comparison with normal diet, but also in comparison with standard ONS. A current meta-analysis of available data from 16 randomised studies of surgical patients (n=1387; immunonutrition n=715, controls n=672) with gastrointestinal tumours was aimed at this question [108]. Preoperative use of immunonutrition alone for 5-7 days led to a significant reduction in the incidence of infectious complications in comparison with a normal diet or with an isonitrogenous standard ONS (OR: 0.52; 95% CI: 0.38 to 0.71, $p<0.0001$). The heterogeneity of the data was low (I^2=16%). There was a significant reduction in the length of stay in hospital compared with the normal diet (WMD: -1.57 days, 95% CI: -2.48 to -0.66, $p<0.001$, I^2=34%) although this did not reach significance when compared with the standard ONS. The rate of non-infectious complications and mortality were without difference [108]. The results of this meta-analysis with a focus on surgical patients with gastrointestinal cancer revealed good quality trials and acceptable heterogeneity suggesting that oral supplementation carried out exclusively preoperatively for 5 days is effective and that immunonutrition may be superior in comparison with standard ONS [108]. Focusing on patients with oesophageal resection in particular, another meta-analysis of 15 randomised studies (1864 patients) confirmed the benefits of immunonutrition over standard nutrition on the rate of infectious complication and length of stay [109]. Current ESPEN guidelines on clinical nutrition in surgery recommend the intake of ONS before major surgery for 5-7 days, with incorporation of immunomodulating supplements being preferred [4].

10.2 Parenteral glutamine

Glutamine supplementation may lead to a reduction in bacterial translocation from the gut, improved immune cell function, decreased proinflammatory cytokine production, and increased antioxidant capacity. There is an ongoing debate regarding glutamine supplementation. In a recent meta-analysis 31 prospective randomised studies with 2201 patients undergoing surgery for colorectal cancer were included [110]. Glutamine was administered in 23 studies via the parenteral in 8 via the enteral route. The patients in the glutamine group had a significantly decreased rate of surgical site infections (RR = 0.48, 95% CI: 0.30–0.75, p=0.001), anastomotic leakage (RR = 0.23, 95% CI: 0.09–0.61, p=0.003), and hospital length of stay (SMD = −1.13, 95% CI: −1.68 to −0.58, p=0.000) [110].

Ziegler et al. [111] investigated the safety and effect of parenteral administration of glutamine in a standard dose of 0.5 g/kg/day in a multi-centre, double-blind study of surgical intensive care patients (n=150) where enteral nutrition was advanced in combination with parenteral nutrition. There were no safety risks, but no significant differences in hospital mortality and infection rate were observed. A meta-analysis of 19 randomised clinical trials with 1243 participants undergoing major abdominal surgery showed that glutamine supplementation did not affect over morbidity or infectious complications [112]. However, the trials included were underpowered and of medium or low quality [112]. Overall, the current ESPEN guideline on clinical nutrition in surgery is based on weak evidence and conclusions were based limited based on studies of parenteral nutrition thus glutamine supplementation should only be considered for surgical patients with specific prior indication for parenteral nutrition [4].

10.3 Parenteral omega-3-fatty acids

In a meta-analysis of 49 randomised studies that compared parenteral nutrition enriched with omega-3 fatty acids with a standard lipid solution, clinical advantages of supplementation were again shown. The risk of infection was 40% lower (24 studies: RR: 0.60; 95% CI: 0.49 to 0.72; p<0.00001) and mean duration of intensive care stay was significantly shorter (10 studies: 1.95 days; 95% CI: 0.42 to 3.49; p=0.01). This also applied to the length of stay in hospital (26 studies: 2.14 days; 95% CI: 1.36 to 2.93, p<0.00001). The risk of a septic course was also 56% lower (9 studies: RR=0.44; 95% CI: 0.28 to 0.70, p=0.0004). The mortality rate was not significantly reduced by 16% (20 studies: RR=0.84; 95% CI: 0.65 to 1.07, p=0.15) [113]. Notably, the heterogeneity (I^2: 83%) of the studies should be considered.

The ESPEN guidelines on clinical nutrition in surgery gives a recommendation of "B" for the inclusion of omega-3 fatty acids in parenteral nutrition of patients who cannot receive adequate enteral nutrition and therefore already require parenteral nutrition [4]. This has been confirmed at an international consensus conference where it was agreed that lipids are an integral part of parenteral nutrition although a dosage of 1.5 g/kg body weight should not be exceeded [114]. Thus, in surgical patients with an indication for parenteral nutrition, solutions enriched with omega-3 fatty acids offer clinical advantages over standard solutions and should be used whenever possible [4, 114].

11. Does nutritional therapy make a difference for all or for a select few?

Nutrition is vital for all hospitalised patients, regardless of surgical status. Data from nutritionDay [115] showed that patients who ate 50% of the recommended amount while in hospital had a much lower risk of death compared with patients who did not consume any of the offered food [3]. Nutrition support beyond regular hospital tray service should be based on individual patient status, especially when considering the duration of therapy prescribed [4]. For example, in severely malnourished patients, nutritional support alone may not sustain muscle during the postoperative phase but can support the body’s response to surgical trauma [4]. Hence, nutritional risk should be assessed, at minimum, pre- [5] and postoperatively to ensure that adequate nutritional support is provided [4].

Surgical patients often exhibit phenotypes that negatively impact muscle (i.e., low muscle mass, malnutrition) and are associated with poor postoperative outcomes [3]. The synergistic effect of individual nutrients (e.g., amino acids and derivates, fish oil/ eicosapentaenoic acid) on muscle quantity and quality is an area of the literature that requires further investigation [83, 116]. Regardless, nutritional recommendations often focus on protein, which is essential for muscle health, especially during recovery, although optimal protein intake for the surgical population remains undefined [5]. Given that surgery induces stress, protein guidelines for the critically-ill (1.2-2.0 g/kg/d actual body weight) [117] may be used as a starting point [5] although optimal protein intake is estimated to be 1.5g/kg/d [4, 118]. Protein should be distributed across meals (~25-35 g/meal) and focus on high quality (animal-based) sources [5], especially for people with cancer [119]. Attaining protein recommendations should be the top nutritional priority pre- and postoperatively, followed by energy intake goals [5]. β-hydroxy β-methylbutyrate (HMB) is another nutrient of interest for muscle health. A recent systematic review found that HMB supplementation has a beneficial effect on muscle mass and function and on surgical complications when provided to oncology patients in the preoperative and postoperative phases [120].

The impact of preoperative nutritional status on postoperative morbidity and mortality is well documented as previously discussed. Nutritional deficits should be replenished, and overall nutritional status optimised throughout the perioperative period, especially in the preoperative phase [86]. If protein and energy needs are not obtained by oral intake alone for a period of 7 days, additional nutritional interventions need to be initiated via enteral and/or parenteral nutrition [5]. If nutritional assessment reveals that the patient is malnourished or at risk of malnutrition, formulae containing immunonutrients should be provided [3-5]. In cancer, immunonutrition administered preoperatively resulted in significantly less complications and decreased length of stay compared with standard ONS [108].

Overall, optimal nutrition is vital to all patients but is critical in those who are deemed to be at nutritional risk or malnourished prior to surgery [3-5]. Several nutrition-related therapy modalities are under consideration for the surgical patient, as summarized in **Figure 3**. A scoping review on ongoing trials investigating the impact of nutritional interventions on muscle-related outcomes noted several ongoing studies in various surgical settings (e.g., cancer, bariatrics, kidney disease) [121]. Although heterogeneity of trial protocols precludes a comprehensive understanding of specific effects on operative outcomes, to improve patient outcomes, nutritional support should be initiated preoperatively and continued postoperatively until the patient is no longer at risk. In patients who are well nourished perioperatively, high-protein ONS may still be recommended upon hospital discharge to ensure that protein and energy needs are met during recovery in the community, especially if needs are unlikely to be met by food alone [3, 5].

12. Personalised nutrition

Currently, there are only few studies looking at the potential of personalised nutrition in the surgical patient. The term "personalised medicine" relates to the observation that not all patients show the same response to medical therapies [122]. For example, while some patients may show a marked benefit from nutritional therapy, other patients may receive no benefit or may even suffer harm from that intervention [123]. Whether or not a patient benefits from nutritional therapy may relate to illness-specific factors (e.g., type of surgery, type of tumour in oncology patients, comorbidities, acute versus chronic course, high versus low inflammation) or patient-specific factors (e.g., age and ethnicity). Additionally, there are several studies suggesting that specific biomarkers and metabolomic signatures may allow us to identify patients that will or will not benefit from nutritional therapy — or help to select patients for specific nutritional interventions [123]. Such markers will promote the use of more individualised nutritional therapy, especially in patients with high probability that nutritional therapies will have the most effect. For medical inpatients, secondary analyses from the randomised-controlled, multi-centre EFFORT trial [124] that included over 2000 patients in 8 Swiss hospitals suggested that patients with high inflammation (versus low or moderate inflammation) acquired less benefit from nutritional therapy [123], while albumin concentrations and several metabolomic markers were not associated with the nutritional response [125, 126]. Interestingly, there was a strong association between low admission serum albumin concentrations and an adverse clinical course, but patients with low albumin did not show more benefit from nutritional support demonstrating that nutritional biomarkers may have prognostic implications but may not be useful for selecting patients regarding nutritional treatment [126]. Other secondary analyses of the EFFORT trial [124] found that hand-grip strength [127] and stratification by the GLIM criteria [128] provided modest information on the potential benefit of treatment. Whether these associations are also true for the surgical patient remain largely unknown today and future research is needed to better phenotype the surgical patient in need of nutritional support to be most effective in treating malnutrition.

13. Conclusion

Nutritional status is a critical aspect of overall patient status that should be considered, and optimised, throughout the perioperative period. Despite advances and further integration of nutritional screening, assessment, and optimisation, patients continue to go through surgery without consideration of nutritional status. Standardised processes are needed to promote widespread integration of evidence-based, nutrition-related surgical guidelines and pathways. Future research should focus on contentious topics of perioperative nutrition to provide further insight into best practices.

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K.L.F and D.N.L. have no conflicts to declare.

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Author contributions

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Legends for Figures

Figure 1: Select contentious areas in perioperative nutrition, their impact on patients, and suggestions for improvements in patient care.

Figure 2: Marginal gains theory applied to perioperative nutritional therapy. Small gains acquired throughout the surgical continuum may result in clinically meaningful improvements in surgical outcomes.

Figure 3: Summary of selected nutrition-related therapies under consideration for optimising nutritional status of the surgical patient.

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Table 1: Characteristics of selected nutrition screening tools for adults.

Nutrition screening tool	**Parameters included in the tool**	**Recommended settings for use**	**Example of validation in the surgical patient population**
Nutrition Risk Screening (NRS) 2002 [13]	Weight loss Recent food intake Body mass index and impaired general condition Severity of disease Age	Adults admitted to hospital	Compared with SGA in n=300 surgical patients [15] Sensitivity: 0.8 (0.76-0.84) Specificity: 0.89 (0.84-0.92) PPV: 87% NPV: 100%
Malnutrition Universal Screening Tool (MUST) [16]	Weight loss Body mass index Reduced food intake for ≥5 days (acute disease)	Community dwelling adults Adults admitted to hospital and	Compared with SGA in n=300 surgical patients [15] Sensitivity: 0.85 (0.79-0.87) Specificity: 0.93 (0.87-0.95) PPV: 89%

		other care settings	NPV: 99%
Mini Nutritional Assessment Short-Form (MNA-SF) [17]	BMI Recent weight loss (>1kg) Acute illness or stress Housebound Dementia or depression Appetite loss or eating difficulty	Older adults living in institutional settings Community dwelling older adults	Compared with MNA in n=408 surgical patients who were older adults [18] For assessing malnutrition: Sensitivity: 100% Specificity: 69.5% PPV: 19.4% NPV: 100%
Malnutrition Screening Tool (MST) [19]	Unintentional weight loss Appetite	Adults admitted to hospital	Compared with SGA in n=100 surgical patients [20] Sensitivity: 54% Specificity: 25% Concordance kappa coefficient: 0.90 ($p \leq 0.0001$)

Short Nutritional Assessment Questionnaire (SNAQ) [21]	Unintentional weight loss Decreased appetite Use of supplemental drinks or tube feeding	Adults admitted to hospital	Original validation study performed in n=297 patients admitted to internal (47.8%) or surgical (52.2%) wards [21] For assessing moderate and severe malnutrition: Sensitivity: 79% Specificity: 83% PPV: 70% NPV: 89%
Subjective Global Assessment (SGA) [22]	Weight loss Reduced food intake Gastrointestinal symptoms Functional capacity	Adults admitted to hospital Community dwelling adults	Originally validated in n=59 surgical patients against objectives markers of nutritional status to predict clinical outcomes [23]

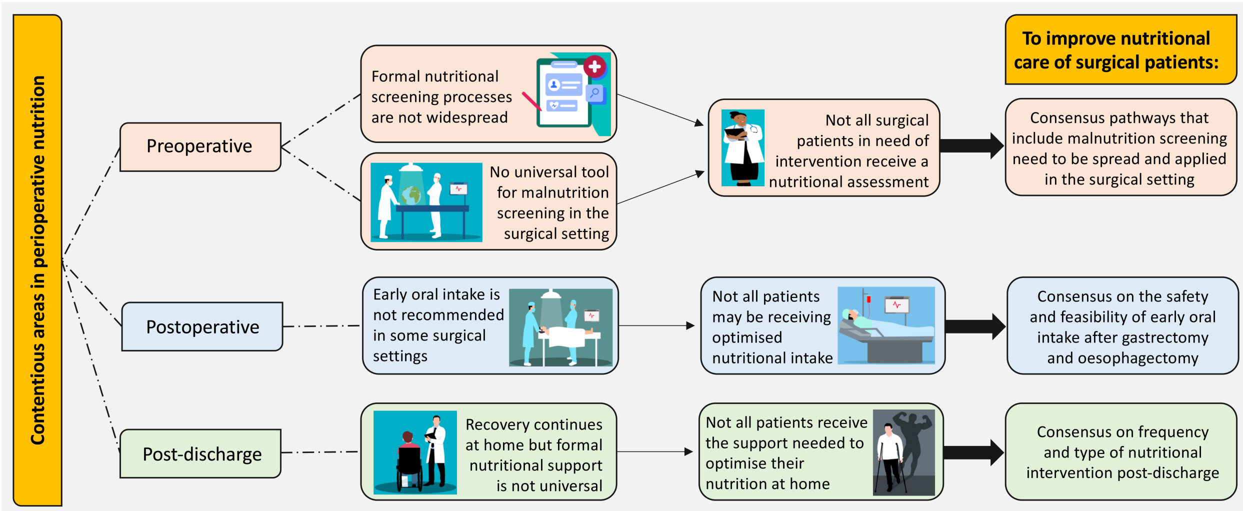
	Comorbid illness and its relation to nutritional requirements Brief physical examination		
Perioperative Nutrition Screen (PONS) [5]	Low BMI Reduced food intake Weight loss Low albumin concentration	Adult patients preoperatively before elective surgery	Preoperative nutritional risk assessed by PONS in n=3151 patients predicted risk of adverse postoperative complications independent of a validated malnutrition diagnosis [24]

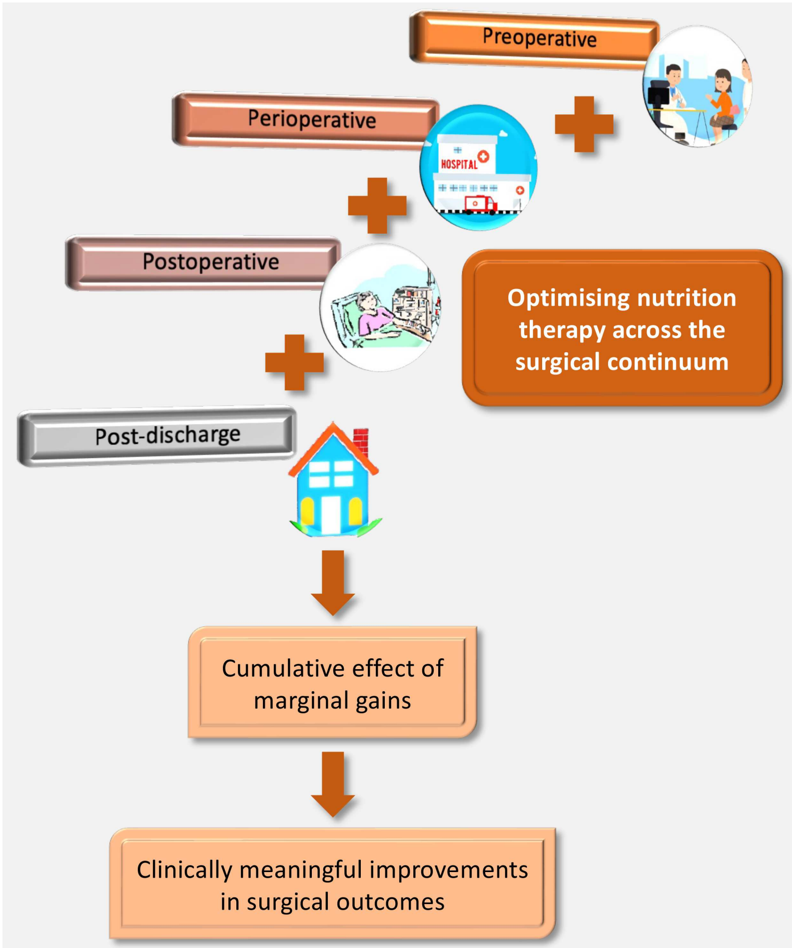
BMI: body mass index; NPV: Negative predictive value; PPV: Positive predictive value

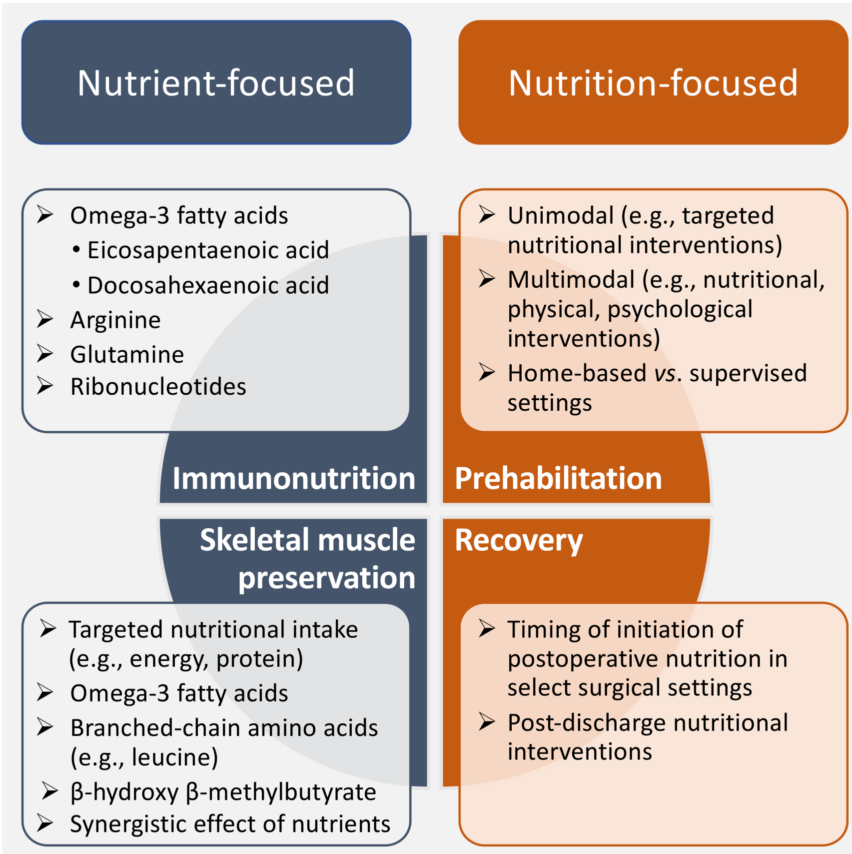
Table 2. Summary of selected systematic reviews and meta-analysis investigating the impact of preoperative interventions (prehabilitation) on postoperative outcomes

Authors	**Study population**	**Number of studies (patients) included**	**Preoperative interventions**	**Postoperative outcomes of interest**	**Main findings**
Daniels, *et al*. [57]	Older adults undergoing elective surgery for abdominal cancer	33 (3362)	Exercise Nutrition Psychological input Geriatric assessment Smoking cessation Multimodal	Complication rates Length of hospital stay	Multimodal and nutrition interventions showed significant benefit to rate of postoperative complications. No difference to length of hospital stay was observed.
Assouline, *et al*. [58]	Adults undergoing elective surgery	29 (2070)	Exercise	Pulmonary complications	Preoperative exercise reduced postoperative pulmonary

				Length of hospital stay Mortality	complications and hospital length of stay. No difference was seen for mortality.
Waterland, *et al*. [59]	Adults undergoing surgery for abdominal cancer	22 (1700)	Exercise Respiratory Nutrition Psychological Education	Complications Length of hospital stay Readmission Mortality	Preoperative interventions reduced hospital length of stay but no effect was seen for postoperative complications including pulmonary complications, hospital readmission, or mortality.


Contentious areas in perioperative nutrition
Preoperative
Postoperative
Post-discharge
Formal nutritional screening processes are not widespread
No universal tool for malnutrition screening in the surgical setting
Not all surgical patients in need of intervention receive a nutritional assessment
To improve nutritional care of surgical patients:
Consensus pathways that include malnutrition screening need to be spread and applied in the surgical setting
Early oral intake is not recommended in some surgical settings
Not all patients may be receiving optimised nutritional intake
Consensus on the safety and feasibility of early oral intake after gastrectomy and oesophagectomy
Recovery continues at home but formal nutritional support is not universal
Not all patients receive the support needed to optimise their nutrition at home
Consensus on frequency and type of nutritional intervention post-discharge


Preoperative
Perioperative
HOSPITAL
Postoperative
Optimising nutrition therapy across the surgical continuum
Post-discharge
Cumulative effect of marginal gains
Clinically meaningful improvements in surgical outcomes



Nutrient-focused
Nutrition-focused
Omega-3 fatty acids
• Eicosapentaenoic acid
• Docosahexaenoic acid
Arginine
Glutamine
Ribonucleotides
Immunonutrition
Unimodal (e.g., targeted nutritional interventions)
Multimodal (e.g., nutritional, physical, psychological interventions)
Home-based vs. supervised settings
Prehabilitation
Skeletal muscle preservation
Targeted nutritional intake (e.g., energy, protein)
Omega-3 fatty acids
Branched-chain amino acids (e.g., leucine)
β-hydroxy β-methylbutyrate
Synergistic effect of nutrients
Recovery
Timing of initiation of postoperative nutrition in select surgical settings
Post-discharge nutritional interventions